UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,452	10/31/2000	David B. Weiner	UPAP-0404	6483

34137 7590 12/08/2003

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 12/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/622,452	WEINER ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,9-15,17,18,20-22 and 33-36* is/are pending in the application.

4a) Of the above claim(s) *20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,9-15,17,18 and 33-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6, 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response to the notice of non-responsive amendment has been entered. Claims 5, 8, 16, 19, 23,-32, and 37-39 have been canceled. Claims 1-4, 6-7, 9-15, 17-18, 20-22, and 33-36 are currently pending in the instant application at this time. Of these, claims 20-22 are withdrawn as being directed to subject matter non-elected without traverse in paper no. 14. Claims 1-4, 6-7, 9-15, 17-18, and 33-36 are currently under examination. An action on the merits follows.

Restriction/Election

Applicant's election without traverse of the subject matter of group I is acknowledged. The applicant's further election of the species "plasmid" for a nucleic acid, and the species "DR5" for immunomodulatory protein is also acknowledged. Based on applicant's election of the species "DR5" as the immunomodulatory protein, claims 20-22, which depend on canceled claim 19 (see below), are directed to non-elected species IL-8, RANTES, LFA-3, and CD40L, and thus have been withdrawn from examination. Further, please note for the record that although the claims 33-36 continue to broadly recite "nucleic acids" and claims 1-4, 6-7, 9-15, 17-18, and 33-36 include markush groups of immunomodulatory proteins not limited to the elected species, this application has been examined based on the elected species of "plasmids" and "DR5".

Priority

The applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). While the applicant does make a specific claim of priority to parent application 60/076,207, this reference appears on page 1, line 10, of the specification under the heading "Background of the Invention". In order to perfect the applicant's claim of priority, the priority claim must appear as the first sentence of the specification, preferably under the heading , "Cross-Reference to Related Applications ". See MPEP 6.01.

Nucleotide and/or Amino Acid Sequences

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. In particular, please note that the specification fails to include a SEQ ID NO for amino acid

sequence listed on pages 31. The applicant is further encouraged to check the specification for further examples of nucleotide or amino acid sequences that do not reference a SEQ ID NO.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules and a response to the rejections set forth below. Failure to comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-7, 9-15, 17-18, and 33-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The applicant claims methods of inducing an immune responses in an individual against an immunogen comprising administering one or more plasmids which encode an immunogen and an "immunomodulating" molecule such as DR5. The applicant also claims methods of immunizing an individual against herpes simplex virus infection by administering one or more plasmids encoding herpes simplex antigen HSV2gD and an "immunomodulating" molecule such as DR5. The applicant also claims a single plasmid

encoding an immunogen and DR5 or a composition of two plasmids wherein the first plasmid encodes an immunogen and the second plasmid encodes DR5. In regards to the product claims, claims 1-4, 6, 9-10, 12-15, and 17, please note that these claims have been included in the instant rejection based on the disclosed use of these plasmids for inducing immune responses in an individual. Please note as well that the instant grounds of rejection are based on applicant's elected species of "immunomodulatory" protein, which is DR5.

The specification broadly discloses the use of a single plasmid encoding an immunogen and an "immunomodulatory" protein or a combination of a first plasmid encoding an immunogen and a second plasmid encoding an "immunomodulatory protein" for inducing immune responses *in vivo*. The specification generally discloses numerous immunogens and "immunomodulatory" proteins which can be used in the disclosed plasmids and compositions. The immunogens include pathogenic antigens, cancer-associated antigens, and antigens linked to cells associated with autoimmune disease. The specification lists examples of these different types of antigens including HIV or HSV antigens as pathogenic antigens, p53 and ras for cancer-associated antigens, and various T cell receptors as antigens linked to cells associated with autoimmune disease. In all such cases, the specification clearly indicates that the purpose of the invention is to generate antigen specific immune responses against the encoded immunogen in order to treat or prevent the associated disease or infection. In regards to "immunomodulatory" proteins, the specification likewise lists a large number of genes, including the death receptor DR5. The specification, however, does not provide any specific guidance as to particular immunogens to be combined with DR5 or provide any specific guidance concerning the use of DR5 as an immunogen.

The specification, while providing a reference to the sequence of DR5 on page 85 of the specification, fails to provide an enabling disclosure for the use of DR5 as an "immunomodulatory" protein or for the generation of any type of immune response following administration of plasmids encoding DR5 and an immunogen. DR5, also known as TRAIL-R2 and KILLER, is a death-domain containing receptor which binds to the TRAIL ligand. DR5 was independently cloned by various groups in 1997 (see for instance MacFarlane et al. (1997) J. Biol. Chem., Vol. 272 (41), 25417-25420 and Sheridan et al. (1997) Science, Vol. 277, 818-821). DR5 was not extensively characterized prior to the effective filing date of the instant application. At the time of filing, the art reported that DR5 is a member of a family of receptors that bind TRAIL and which are capable of inducing apoptosis. MacFarlane et al. and Sheridan et al. both reported that ectopic expression of DR5 in certain human cells results in apoptosis and speculate that ligand binding between TRAIL and DR5 may lead to cell death *in vivo* (MacFarlane et al., page 25417, and page 25419, Figure3; Sheridan et al., page 818, and page 820, Figure 3). The TRAIL/DR5 interaction, however, is further complicated by additional receptors for TRAIL including decoy receptors which appear to inhibit TRAIL mediated signaling through DR5 (Sheridan et al., page 820, Figure 4). Thus, due to the existence of decoy receptors for TRAIL, the skilled artisan would not have been able to predict without undue experimentation whether expression of DR5 in a cell that also expresses a decoy receptor would even result in apoptosis. Summarizing the teachings of the prior art concerning DR5, it appears that while the literature at the time of filing does suggest a role for DR5 in regulating cell death, there is no indication that DR5 acts in any way as an "immunomodulatory" protein. DR5 is not preferentially expressed in any type of immune cells and does not appear to have any activity which would result in

activation or upregulation of immune responses following antigen exposure. Therefore, based on the nature of DR5 as an inducer of apoptosis, the skilled artisan would not have been able to predict without undue experimentation whether the co-expression of an antigen and DR5 in a cell would in fact be capable of stimulating T cells, B cells, or any other type of immune effector cells.

The specification does not provide any guidance which supplements the knowledge present in the prior art concerning DR5. While the specification does in fact provide a number of examples of the broader invention relating to the ability of proteins such as ICAM, LFA-1, and GM-CSF to modulate the immune response to model antigens, the specification does not provide any specific guidance for the use of DR5 as an "immunomodulatory" protein. As discussed in detail above, DR5 is an inducer of apoptosis and does not have any known "immunomodulatory" properties. Further, DR5 is not related structurally or functionally to the immunostimulatory molecules exemplified in the working examples such that a correlation can be made between the activity of the cytokines and chemokines utilized in the working examples and DR5. In fact, based on the apoptotic properties of DR5 as reported by Sheridan et al. and MacFarlane et al., the skilled artisan might predict that cells transfected with an antigen and DR5 would undergo apoptosis before they even had an opportunity to engage an immune effector cell, thereby precluding any effect on immune responses to the immunogen. Therefore, in view of the nature of the DR5 molecule as reported in the prior art of record, the lack of particular guidance concerning how to use the DR5 molecule to stimulate or enhance immune responses to immunogen, the lack of working examples which utilize proteins that correlate to DR5, and the

breadth of the claims, it would have required undue experimentation to use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) The invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-3, and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by MacFarlane et al. (1997) J. Biol. Chem., Vol. 272 (41), 25417-25420. The applicant claims a single plasmid encoding an immunogen and DR5 or a composition comprising a plasmid encoding DR5 and a plasmid encoding an immunogen.

MacFarlane et al. teaches a single plasmid encoding the bacterial immunogen beta-galactosidase (lacZ) operatively linked to the RSV promoter and DR5 operatively linked to the CMV promoter(MacFarlane et al., page 25418, paragraph 1, and page 25419, Figure 3). MacFarlane et al. further teaches a composition comprising two plasmids, where the first plasmid encodes an immunogen such as CrmA or FLAME-1 and the second plasmid encodes

DR5 (MacFarlane et al., page 25418, paragraph 1, and page 25419, Figure 3). Thus, by teachings all the elements of the claims as written, MacFarlane et al. anticipates the instant invention as claimed.

Claims 1-3, 6, and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,417,328 (7/9/02), hereafter referred to as Alnemri. The applicant claims a single plasmid encoding an immunogen and DR5, and an injectable pharmaceutical solution of the plasmid. The applicant also claims a composition comprising a plasmid encoding DR5 and a plasmid encoding an immunogen.

Alnemri teaches a single plasmid encoding the bacterial immunogen beta-galactosidase (lacZ) operatively linked to the RSV promoter and DR5 operatively linked to the CMV promoter (Alnemri, column 27, lines 14-21). Alnemri further teaches a composition comprising two plasmids, where the first plasmid encodes an immunogen such as CrmA or FLAME-1 and the second plasmid encodes DR5 (Alnemri, column 27, lines 14-21, and column 28, lines 47-53). Alnemri also teaches injectable pharmaceutical compositions of the nucleic acids (column 22, lines 12-59). Thus, by teaching all the limitations of the claims as written, Alnemri anticipates the instant invention as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be

reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Please note that the United States Patent and Trademark Office will begin to move to the new campus in Alexandria, Virginia, in December 2003. The examiners of Art Unit 1632 will be moving in January 2004. As of January 13, 2004, this examiner's phone number will be (571) 272-0737, and that of the examiner's supervisor will be (571) 272-0734.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER